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STOUT, UXA, BUYAN & MULLINS LLP			GOLDBERG, JEANINE ANNE	
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IRVINE, CA 92618			ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,825	WALLACE ET AL.	
	Examiner	Art Unit	
	JEANINE A. GOLDBERG	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 21 March 2012.
 2a) This action is **FINAL**. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1,2 and 13-17 is/are pending in the application.
 4a) Of the above claim(s) 2 is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 1 and 13-17 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ . |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ . | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| | 6) <input type="checkbox"/> Other: _____ . |

DETAILED ACTION

1. This action is in response to the papers filed June 21, 2010. Currently, claims 1-2, 13-17 are pending. Claim 2 has been withdrawn as drawn to non-elected subject matter.
2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 21, 2012 has been entered.
3. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.
4. Any objections and rejections not reiterated below are hereby withdrawn.
5. This action contains new grounds of rejection.

Election/Restrictions

6. Applicant's election without traverse of the species of T4141G Mutation and Alzheimer 's disease, in the paper filed June 21, 2010 is acknowledged.

In a telephone interview on August 17, 2010, the Examiner called Robert Buyan to request clarification regarding the T4141G mutation. The specification and the art teach a T414G mutation. In the telephone interview Mr. Buyan requested the examiner treat the election as T414G rather than T4141G.

Claim 2 has been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

The requirement is still deemed proper and is therefore made FINAL.

Priority

7. This application claims priority as a 371 to PCT/US05/10266, filed March 29, 2005 and provisional application 60/557,612, filed March 29, 2004.

Drawings

8. The drawings are acceptable.

Information Disclosure Statement

9. The information disclosure statement filed March 21, 2012 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Improper Markush Grouping

10. Claim 1 is rejected under the judicially approved “improper Markush grouping” doctrine. (See Federal Register, Vol. 76, No. 27, Wednesday, February 9, 2011, page 7166). This rejection is appropriate when the claim contains an improper grouping of alternatively useable species. See *In re Harnisch*, 631 F.2d 716, 719–20 (CCPA 1980).

A Markush claim contains an “improper Markush grouping” if: (1) the species of the Markush group do not share a “single structural similarity,” or (2) the species do not share a common use. Members of a Markush group share a “single structural similarity” when they belong to the same recognized physical or chemical class or to the same art-recognized class. Members of a Markush group share a common use when they are disclosed in the specification or known in the art to be functionally equivalent.

See MPEP § 803.02.

Here the species are directed to methods for detecting T414C and methods for detecting T477C.

The recited alternative species in the groups set forth here do not share a single structural similarity, as each different polymorphic position that could be detected is itself located in a separate region of the genome and has its own structure. The nature of polymorphic structures is that they are differences within a population. The flanking nucleotides surrounding each polymorphic location have a unique sequence relative to the others- they are not structurally the same when you consider the sequence required to identify one particular polymorphic position relative to another polymorphic position. The polymorphic markers recited in the instant claims, and the methods which detect them, do not share a single structural similarity since each consists of a different nucleotide alteration that occurs at a different location on the mtDNA. The only structural similarity present is that all detected positions are part of nucleic acid molecules. The fact that the markers comprise nucleotides per se does not support a conclusion that they have a common single structural similarity because the structure of comprising a nucleotide alone is not essential to the common activity of being correlated with neurodegenerative disorders. For

example, the polymorphism of a T or C at position 414 has a distinct chemical structure as compared to, for example, a polymorphism of a T or C at 477 since the variant position can only be understood within the context of the surrounding nucleotides, which are structurally dissimilar. Accordingly, while the different markers are asserted to have the property of being indicative of neurodegenerative disorders, they do not share a single structural similarity.

Following this analysis, the claims are rejected as containing an improper Markush grouping.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

11. Claims 1, 13-17 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The unpatentability of laws of nature was confirmed by the U.S. Supreme Court in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, No. 10-1150 (March 20, 2012).

Based upon consideration of all of the relevant factors with respect to the claim as a whole, the claims are held to claim law of nature, and is therefore rejected as ineligible subject matter under 35 U.S.C. 101. The rationale for this finding is explained below:

The unpatentability of laws of nature was confirmed by the U.S. Supreme Court in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, No. 10-1150 (March 20, 2012). “[L]aws of nature, natural phenomena, and abstract ideas” are not patentable. *Diamond v. Diehr*, 450 U. S. 175, 185 (1981); see also *Bilski v. Kappos*, 561 U. S. ___, ___ (2010) (slip op., at 5).

“Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work.”

Gottschalk v. Benson, 409 U. S. 63, 67 (1972). The Supreme Court does acknowledge that it is possible to transform an unpatentable law of nature, but one must do more than simply state the law of nature while adding the words “apply it.” See, e.g., *Benson, supra*, at 71–72.

Claim 1 is directed to a method for determining whether a human or animal subject is at risk of developing a neurodegenerative disorder by determining the mtDNA CR mutation of T414C in samples.

The instant claims set forth laws of nature- namely relationships between the presence of mutations and risk of developing neurodegenerative disorders. An application that simply describes that relation sets forth a natural law. The additional steps in the claimed method (i.e., determining mutations) are not themselves natural laws, but neither are they sufficient to transform the nature of the claims.

In the instant case, the claims inform a relevant audience about certain laws of nature. The additional steps consist of well-understood, routine, conventional activity already engaged in by the scientific community. The additional steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately. The Court has made clear that to transform an unpatentable law of nature into a patent-eligible *application* of such a law, one must do more than simply state the law of nature while adding the words "apply it." Essentially, appending conventional steps, specified at a high level of generality, to laws of nature, natural phenomena, and abstract ideas cannot make those laws, phenomena, and ideas patent-eligible.

In *Prometheus*, the Court found that “[i]f a law of nature is not patentable, the neither is a process reciting a law of nature, unless that process has additional features that provide practical assurance that the process is more than a drafting effort designed to monopolize the law of nature itself.” Additionally, “conventional or obvious” “[pre]solution activity” is normally not sufficient to transform an unpatentable law of nature into a patent-eligible application of such a law”. *Flook*, 437 U. S., at 590; see also *Bilski*, 561 U. S., at ____ (slip op., at 14) (“[T]he prohibition against patenting abstract ideas ‘cannot be circumvented by’ . . . adding ‘insignificant post-solution activity’” (quoting *Diehr*, *supra*, at 191–192)).

The Court also summarized their holding by stating “[t]o put the matter more succinctly, the claims inform a relevant audience about certain laws of nature; any additional steps consist of well understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately.”

For these reasons the claims are rejected under section 101 as being directed to non-statutory subject matter.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1, 13-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for determining the presence of mtDNA CR

mutations, does not reasonably provide enablement for a method for diagnosis of any disorder associated with the development of beta amyloid deposits or fibrils, such as Alzheimer's disease, in a human or animal by determining the presence or quantity of mtDNA CR mutations, such as T414G. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims
The claims are drawn to methods for diagnosis of any disorder associated with the development of beta amyloid deposits or fibrils, such as Alzheimer's disease, in a human or animal by determining, by quantifying, the presence or quantity of mtDNA CR mutation of T414G and comparing a mtDNA value to a mtDNA value representative of subjects who suffer from a disorder associated with the development of beta amyloid deposits or fibrils.

Claims to diagnosis require a reliable association between the genotype and the phenotype.

The invention is in a class of invention which the CAFC has characterized as “the unpredictable arts such as chemistry and biology.” Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches the detection of mtDNA control region mutations as a diagnostic for disorders associated with the development of beta amyloid deposits or fibrils in a human or animal is unpredictable at the time the invention was made.

Murdock et al. (Nucleic Acids Research, Vol. 28, No. 21, pages 4350-4355, 2000) teaches age-related accumulation of the T414G mitochondrial DNA control region mutation in muscle, but not in brain. Murdock analyzes the mtDNA using a sensitive PNA-directed PCR clamping based method. In particular the T414G mtDNA mutation was analyzed in both human skeletal muscle and brain samples for the accumulation of the mutation with age (page 4351, col. 1). The relative quantities of mtDNA were measured using competitive PCR (page 4351, col. 2). As seen in Figure 2, PNA-clamping blocks wild-type, but not mutant, molecule amplification to prevent false positive amplification (page 4352, col. 1). To increase the sensitivity of the PNA-clamped reaction, a second round of PCR on diluted product from the first reaction may be performed using restriction enzyme digestion (page 4352, col. 2-4353, col. 1). Murdock concludes that PNA-clamped reactions can be multiplexed to allow simple and efficient identification of multiple mtDNA mutation in diagnosis of mtDNA disease (page 4351, col. 2). The PNA-clamping also permits low levels of heteroplasmy mutations to be detected at a ratio of 1:100. Thus, the control region mtDNA mutation T414G was found in skin fibroblasts from older human subjects and also accumulates in skeletal muscle after age 35 years (page 4354, col.

1). The T414G mutation could not be detected in any human brain sample, even from subjects as old as 93 years (page 4354, col. 1).

Chinnery et al. (Am. J. Hum. Genetics, Vol. 68, pages 529-532, published electronically December 21, 2000) teaches determining the presence of mtDNA control region (CR) mutations. In particular Chinnery studied the mtDNA control region in brain tissue from 31 normal elderly individuals, from 35 individuals who had Alzheimer disease and from 47 individuals who had dementia with Lewy bodies. Chinnery teaches postmortem control brain tissue was collected. Chinnery teaches sequencing nucleotides 33-785 of the control region which included the T414G mutation using primer extension reactions and electrophoresis (page 530, col. 1-2). Chinnery fails to detect the T414G polymorphism in any of the 113 samples of brain DNA, either control or individuals with AD. It is unpredictable how the skilled artisan would diagnose AD based upon the T414G polymorphism.

Simon et al. (Genomics, Vol. 73, pages 113-116, 2001) teaches screening for the T414G mutation in brain-derived mtDNA from 8 Alzheimer's disease patients, 27 Parkinson's disease patients, 4 multiple system atrophy patients and 44 controls. Simon failed to detect the T414G mutation in any of the cases (abstract). Simon teaches sampling brain samples from 4 different regions of the brain (page 114, col. 2). Simon also analyzed blood and fibroblasts and the T414G mutation was absent from these tissues also. Simon suggests that there is a possibility that the T414G mutation may be present in brain regions not examined in their study (page 115, col. 1).

Coskun et al. (PNAS, Vol. 101, No. 29, pages 10726-10731, July 20, 2004), applicant's own work, finds that 65% of the AD brains harbored the T414G mutation whereas this mutation was absent from all controls (abstract). Coskun acknowledges the T414G mutation was not detected by others using less sensitive primer extension strategies such as Chinnery.

Howell (Trends in Genetics, Vol. 21, No. 11, pages 583-586, November 2005) considers previous studies performed by Chinnery and Coskun and concludes that the role of mtDNA mutations in the development of AD or PD still remains unestablished (abstract). When considering the results by Coskun, Howell states that the new results of Coskun are inconsistent with previous findings. Howell suggests that the study by Chinnery involved larger number of tissue samples and did not detect the mutation in brains, AD patients or those with dementia and Lewy bodies. Howell suggests the inconsistent findings may be due to different samples of brain tissue. Howell also considers the findings of higher levels of mutations which were not observed by Chinnery. Howell further considers the scientific concerns that mtDNA point mutations are random and independent, how a heteroplasmic somatic mtDNA mutation can reach high levels in the brain tissue of these patients. Howell states that purely on statistical grounds the chances of an mtDNA mutation arising early in the cell lineage that gives rise to the brain will be extremely low. Howell states it is difficult to envisage such a chance event occurring often enough in the human population to account for the prevalence of AD (page 584, col. 2).

Guidance in the Specification.

The specification teaches amyloid fibrils are thought to be involved in the pathogenesis of various amyloid diseases of genetic, infectious and/or spontaneous origin including Alzheimer's disease, spongiform encephalopathies, Parkinson's disease, type II diabetes, Creutzfeldt-Jakob disease, Down's syndrome associated dementia, Huntington's disease, macular degeneration various prion diseases and numerous others. This is a very diverse collection of diseases.

The specification teaches that the mtDNA control region (CR) is a 1000 nucleotide pair, non-coding, region of the mtDNA that contains the promoters for the initiation of heavy (H) and L-strand transcription (PH & PL) (page 2 of the specification). The mtDNA CR encompasses

the light (L) - and heavy (H) strand promoters (Pl and Ph), mtTFA, CSB I, II, and II, Oh1 and Oh2 (page 2 of the specification).

The specification analyzes the total number of heteroplasmic mtDNA CR mutations observed by cloning and sequencing CR clones from AD and control brain samples (page 5, lines 7-10). Figure 3A illustrates the differences between AD and control brains to demonstrate a significant difference. Figure 3B illustrates the difference in patients 80 years and up is significant.

With respect to analysis of the T414G mutation, Example 1 tests for the mutation by PNA clamping PCR in AD brain frontal cortex (page 6 of the specification). The specification sampled a total of 23 AD and 40 control (non-AD) brains (page 9 of the specification). The mutation was found in 65% of the AD brains while none of the normal control brains had the mutation.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to enable the skilled artisan to practice the claimed invention as broadly as claimed.

First the claims are directed to any disorder associated with the development of beta amyloid deposits or fibrils. The specification teaches the genus of disorders encompasses genetic, infectious and/or spontaneous origin including Alzheimer's disease, spongiform encephalopathies, Parkinson's disease, type II diabetes, Creutzfeldt-Jakob disease, Down's syndrome associated dementia, Huntington's disease, macular degeneration various prion diseases and numerous others (see page 2 of the specification). The art teaches the CR mutations

are not associated with Lewy bodies and dementia (see Chinnery, 2000). There is no evidence that diabetes type II patients have any CR mutations at a statistically significant level. The instant specification fails to provide any evidence that all of these disorders are predictably associated with CR mutations. It is unpredictable that each of these distinct disorders is similarly associated with CR mutations absent further unpredictable and undue experimentation.

Second, the claims are directed to both humans and animals. The specification and the art appear to be focused on humans. There are no teachings in the art or the specification whether animals may be diagnosed with disorders associated with the development of beta amyloid deposits or fibrils based upon mtDNA CR mutations. It is unpredictable which mutations, if any mutations are present in animals such as dogs, cat, chimps, rabbits, for example. It is further unpredictable whether these animals accumulated mtDNA mutations in the same manner as humans. Without further, unpredictable and undue experimentation the skilled artisan would be unable to make any diagnosis for dogs, cats, rabbits, chimps regarding mtDNA CR mutations.

Third, with regard to the detection of the mtDNA CR T414G mutation, the prior art teaches the T414G mutation is found in both young and older individuals' fibroblasts (see Michikawa). Murdock teaches the T414G mutation could be detected in muscle from individuals 30 years and older. This suggests that the T414G mutation is found in normal, non diseased individuals. It would be unpredictable that the mere detection of T414G would be indicative of a disorder associated with the development of beta amyloid deposits or fibrils in humans. If the claims were limited to brain tissue samples, it is unpredictable how the skilled artisan could obtain brain tissue to be able to diagnose an individual prior to post mortem in an effective manner.

Fourth, with regard to the particularly elected embodiment of detecting T414G mutation as indicative of Alzheimer's disease, the prior art teaches a lack of association of the mutation

with AD. Murdock teaches that the T414G mutation could not be detected in any human brain sample, even from subjects as old as 93 years (page 4354, col. 1). Chinnery fails to detect the T414G polymorphism in any of the 113 samples of brain DNA, either control or individuals with AD. Simon also analyzed brain-derived mtDNA for the T414G mutation from 8 Alzheimer's disease patients, 27 Parkinson's disease patients, 4 multiple system atrophy patients and 44 controls but failed to detect the T414G mutation in any of the cases. It is unpredictable how the skilled artisan would diagnose AD based upon the T414G polymorphism since the art teaches the T414G mutation is not found in brain tissue or more specifically brain tissue from AD or Parkinson's disease patients. The post-filing date art reviews that studies from Chinnery and Coskun (applicant's work) and concludes the role of mtDNA mutations in the development of either AD or PD still remains to be established. Howell expresses scientific concerns with the frequency at which Coskun detected the mtDNA mutations. In particular Howell stated that the results were inconsistent with previous findings that involved larger number of tissue samples. Howell also rationalized that "purely on statistical grounds, the chances of an mtDNA mutation arising early in the cell lineage that gives rise to the brain will be extremely low. It is difficult to envisage such a chance event occurring often enough in the human population to account for the prevalence of AD." Thus, given the inconsistent results and the scientific rationale provided by Howell, it is unpredictable that the skilled artisan could diagnose AD using the T414G mutation absent further unpredictable and undue experimentation. This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the art teaches the unpredictability of detecting mtDNA CR mutations for diagnosis disorders. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized difficulties of diagnosing disorders based upon mtDNA CR mutations. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection. The response "as explained in the specification, Applicant has determined that the T414C mutations...is present in tissue, cells or body fluid obtained from the subject." This argument has been reviewed but deemed not persuasive. The response fails to address any of the arguments presented above. The specification and the art fail to teach a reliable correlation between the mtDNA CR value in a patient and the mtDNA CR value representative of subjects who suffer from a disorder associated with the development of beta amyloid deposits or fibrils.

As previously argued, the response filed February 22, 2011 fails to address these broad limitations and why the claimed invention is enabled over the full scope of the claims. The response focuses on Example 1 from the specification which is directed to Alzheimer's disease, one particular disorder, in humans, again one member of the genus and T414G mtDNA. This

very narrow embodiment of the instant claims is not representative over the full scope of the claims.

Even though Example 1 is directed to AD, humans and T414G, the art specifically speaks to the study performed by Coskun. As noted in the rejection above, Howell considers the studies performed by Chinnery and Coskun and concludes that the role of mtDNA mutations in the development of AD or PD still remains unestablished (abstract). The response filed on February 22, 2011 fails to consider the teachings in the art regarding the unpredictability of the association of T414G with AD. In particular, Howell states that the new results of Coskun are inconsistent with previous findings. Howell suggests that the study by Chinnery involved larger number of tissue samples and did not detect the mutation in brains, AD patients or those with dementia and Lewy bodies. Howell suggests the inconsistent findings may be due to different samples of brain tissue. Howell also considers the findings of higher levels of mutations which were not observed by Chinnery. Howell further considers the scientific concerns that mtDNA point mutations are random and independent, how a heteroplasmic somatic mtDNA mutation can reach high levels in the brain tissue of these patients. Howell states that purely on statistical grounds the chances of an mtDNA mutation arising early in the cell lineage that gives rise to the brain will be extremely low. Howell states it is difficult to envisage such a chance event occurring often enough in the human population to account for the prevalence of AD (page 584, col. 2). Therefore, it is unpredictable whether the results provided in Example 1 of the specification may be reproduced in a reliable and predictable manner such that ordinary artisan would be enabled to practice the claimed invention of diagnosis of a disorder based upon the quantitative determination of mtDNA.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Newly amended Claims 1, 13-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 1 is indefinite. It is not clear how the recited preamble is intended to breathe life and meaning into the claim. The preamble of Claim 1 is directed to a method for determining whether a human or animal is at risk of developing a neurodegenerative disorder however the claim only provides for determining whether at least one of the mtDNA CR mutations is present. Thus it is not clear if applicant intends to cover any method for determining whether at least one of the mtDNA CR mutations is present, or if the method is intended to somehow require more to accomplish the goal set forth in the preamble. If the claim requires something more, it is unclear what additional active process step the method requires and it appears that the claims are incomplete. The claims fail to provide any active steps that clearly accomplish the goal set forth by the preamble of the claims. Claims 13-17 depend on Claim 1 and are similarly indefinite.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1, 13-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Murdock et al. (Nucleic Acids Research, Vol. 28, No. 21, pages 4350-4355, 2000).

As discussed in the 112/2nd rejection above, the only active method step of the instant claims is directed to determining whether a mtDNA CR mutation of T414C is present in tissue, cells or body fluid obtained from a subject.

Murdock teaches age-related accumulation of the T414G mitochondrial DNA control region mutation in muscle, a tissue. Murdock analyzes the mtDNA using a sensitive PNA-directed PCR clamping based method. In particular the T414G mtDNA mutation was analyzed in both human skeletal muscle and brain samples for the accumulation of the mutation with age (page 4351, col. 1). The relative quantities of mtDNA were measured using competitive PCR (page 4351, col. 2). As seen in Figure 2, PNA-clamping blocks wild-type, but not mutant, molecule amplification to prevent false positive amplification (page 4352, col. 1). To increase the sensitivity of the PNA-clamped reaction, a second round of PCR on diluted product from the first reaction may be performed using restriction enzyme digestion (page 4352, col. 2-4353, col. 1). Murdock concludes that PNA-clamped reactions can be multiplexed to allow simple and efficient identification of multiple mtDNA mutation in diagnosis of mtDNA disease (page 4351, col. 2). The PNA-clamping also permits low levels of heteroplasmy mutations to be detected at a ratio of 1:100. Thus, the control region mtDNA mutation T414G was found in skin fibroblasts from older human subjects and also accumulates in skeletal muscle after age 35 years (page 4354, col. 1). The T414G mutation could not be detected in any human brain sample, even from subjects as old as 93 years (page 4354, col. 1).

Murdock teaches every limitation of the instant claims and thus anticipates the claimed invention.

16. Claims 1, 14-15, 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Chinnery et al. (Am. J. Hum. Genetics, Vol. 68, pages 529-532, published electronically December 21, 2000).

As discussed in the 112/2nd rejection above, the only active method step of the instant claims is directed to determining whether a mtDNA CR mutation of T414C is present in tissue, cells or body fluid obtained from a subject.

Chinnery teaches determining the presence of mtDNA control region (CR) mutations. In particular Chinnery studied the mtDNA control region in brain tissue from 31 normal elderly individuals, from 35 individuals who had Alzheimer disease and from 47 individuals who had dementia with Lewy bodies. Chinnery teaches postmortem control brain tissue was collected. Chinnery teaches sequencing nucleotides 33-785 of the control region which included the T414G mutation using primer extension reactions and electrophoresis (page 530, col. 1-2). Chinnery fails to detect the T414G polymorphism in any of the 113 samples of brain DNA, either control or individuals with AD.

Chinnery teaches every limitation of the instant claims and thus anticipates the claimed invention. The claim only requires determining whether a mutation is present. Chinnery determines a mutation is not present.

17. Claims 1, 14-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Simon et al. (Genomics, Vol. 73, pages 113-116, 2001).

As discussed in the 112/2nd rejection above, the only active method step of the instant claims is directed to determining whether a mtDNA CR mutation of T414C is present in tissue, cells or body fluid obtained from a subject.

Simon teaches screening for the T414G mutation in brain-derived mtDNA from 8 Alzheimer's disease patients, 27 Parkinson's disease patients, 4 multiple system atrophy patients and 44 controls. Simon failed to detect the T414G mutation in any of the cases (abstract). Simon teaches sampling brain samples from 4 different regions of the brain (page 114, col. 2). Simon also analyzed blood and fibroblasts and the T414G mutation was absent from these tissues also.

Simon teaches every limitation of the instant claims and thus anticipates the claimed invention. The claim only requires determining whether a mutation is present. Simon determines a mutation is not present.

Conclusion

18. No claims allowable.

19. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Wang et al. PNAS, Vol. 98, No. 7, pages 4022-4027, March 27, 2001. Wang teaches the T414G mutation was not present in muscle.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Nguyen, can be reached on (571)272-0731.

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The Central Fax Number for official correspondence is (571) 273-8300.

**/Jeanine Goldberg/
Primary Examiner
April 2, 2012**